Living kidney donor evaluation and safety assessment

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CHAPTER 5

Renal Functional Reserve Capacity before and after Living Kidney Donation

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Abstract

Compensatory GFR increase after kidney donation results in a GFR above 50% of the pre-donation value. The Renal Functional Reserve assessed by the renal response to dopamine infusion (RFR_{dopa}) is considered to reflect functional reserve capacity and thought to be a tool for living donor screening. However, it is unknown if the RFR_{dopa} predicts long-term kidney function.

Between 1984 and 2017, we prospectively measured mGFR (^{125}-Iothalamate) and RFR by dopamine infusion in 937 living kidney donors. We performed linear regression analysis of pre-donation RFR_{dopa} and post-donation GFR. In donors with 5-year follow-up after donation we assessed the association with long-term GFR.

Mean donor age was 52±11 years, 52% were female. Mean pre-donation GFR was 114±22 ml/min, GFR_{dopa} was 124±24 ml/min, resulting in a RFR of 9±10 ml/min. Three months post-donation, GFR was 72±15 ml/min and GFR_{dopa} was 75±15 ml/min, indicating that donors still had RFR_{dopa} (3±6 ml/min, P<0.001). Pre-donation RFR_{dopa} was not associated with pre-donation GFR (st. β -0.009, P=0.77), but was positively associated with GFR 3 months after donation (st. β 0.12, P<0.001). In the subgroup of donors with 5-year follow-up data (n=383), RFR_{dopa} was not associated with GFR at 5 years post-donation (st. β 0.05, P=0.35).

In conclusion, RFR_{dopa} is a predictor of short-term GFR after living kidney donation, but not of long-term kidney function. Therefore, measurement of the RFR_{dopa} is not a useful tool for donor screening. Studies investigating long-term renal adaptation are warranted to study the effects of living kidney donation and improve donor screening.

Introduction

Living kidney transplantation is the best available treatment for patients with end-stage renal disease(3, 21). However, due to a persistent shortage of donor organs, the selection criteria for living kidney donors have been liberalized, possibly increasing risks for the prospective living kidney donor(15). This underlines the need for an assessment of living donor kidney function that is as complete as possible, and can reliably predict outcome after donation.

In 1986, measurement of the Renal Functional Reserve (RFR_{dopa}; also called Renal Reserve Capacity), was proposed as a new screening tool for living kidney donors that could possibly increase the number of donors that could safely be accepted for living kidney donation(23–25). The RFR_{dopa} is defined as the increase in Gomerular Filtration Rate (GFR) in response to a vasodilator agent (e.g. dopamine and/or an amino-acid solution) and is considered to reflect the ability of a kidney to increase its filtration when donating a kidney(24). Since the GFR after nephrectomy is 60-75% of its pre-donation value, and not 50% (5, 16, 19, 20), the RFR_{dopa} was thought to be a predictor of renal adaptation after kidney donation(16, 24). In line with this assumption, the RFR_{dopa} has been shown to predict short-term GFR after donation, but to date no prospective data exist on the predictive performance of the pre-donation RFR_{dopa} for GFR measured on the long-term. Also it is unknown if the pre-donation RFR_{dopa} is a predictor of the compensatory GFR increase post-donation (defined as post-donation GFR minus pre-donation single kidney GFR).

Therefore, in this study we investigated the predictive performance of pre-donation RFR_{dopa} on post-donation GFR measured at 3 months and 5 years post-donation. We also investigated if the pre-donation RFR_{dopa} was associated with the compensatory GFR increase post-donation.

Methods

Study design

In this prospective cohort study, we performed renal hemodynamics measurements in 937 living kidney donors, who donated between 1982 and 2017 in the University Medical Center Groningen. We measured mGFR as the urinary clearance of ^{125}I-iothalamate and Renal Functional Reserve (RFR) as the increase of mGFR in response to low-dose dopamine, 4 months before, and 3 months and 5 years after living kidney donation as part of the screening program and post-donation donor evaluation(17, 20). The study was approved by the institutional ethical review board. In 2014, the study of data of the living kidney donor

screening and follow-up in our center was grouped under the TransplantLines biobank and cohort study (NCT0327284) and underwent a renewed ethical review in accordance with current ethical guidelines (METc 2014/077). With its approval, historical clinical data and biobank samples of transplant recipients and donors were cleared for use in research and publications alongside with newly to be collected data and samples of transplant recipients and donors. In our Center, all donors have given consent for the use of their data and samples since the start of our living kidney donation program in 1982. All procedures were conducted in accordance with the declaration of Helsinki, declaration of Istanbul and the Dutch Scientific Guidelines.

Clinical and biochemical measurements

All donors were normotensive or had adequately regulated hypertension (maximum of two antihypertensive drugs). Furthermore, subjects with a history of diabetes (or an abnormal glucose tolerance test), kidney disease or cardiovascular events were excluded from kidney donation. Proteinuria and albuminuria were measured (mg/24h) in routine laboratory measurements from 24-hour urine collection.

Measurement of renal hemodynamics and renal functional reserve

Kidney function was measured using ^{125}I-iothalamate and ^{131}I-Hippuran infusion as described previously(2, 16). Measurements were performed in a quiet room, with the participant in semi-supine position. After drawing a blood sample, ^{125}I-iothalamate and ^{131}I-Hippuran infusions were started (0.04 mL/kg containing 0.04 MBq and 0.03 MBq respectively). At 08.00 hour 0.6 MBq of ^{125}I-iothalamate was administered, followed by continuous infusion of 12 mL/h. After a two-hour stabilization period, baseline measurements were performed in a steady state of plasma tracer levels. Clearances were calculated as (U*V)/P and (I*V)/P, where U*V represents the urinary excretion, I*V represents the infusion rate of the tracer and P represents the plasma tracer concentration per clearance period. From clearance levels of these traces, GFR, effective renal plasma flow (ERPF) and filtration fraction (FF) were calculated. Correction for incomplete bladder emptying and dead space was achieved by multiplying the ^{125}I-iothalamate filtration fraction with plasma ^{131}I-Hippuran clearance. Day-to-day variability of GFR is 2.5%(2). Renal functional reserve (RFR_{dopa}) was measured by extending the procedure mentioned above with two hours of a 1.5 µg/kg/min of dopamine infusion(22). The RFR_{dopa} is then calculated as:

RFR_{dopa} (mL/min) = $GFR_{dopamine} - GFR$

The compensatory mGFR increase after donation is calculated as:

mGFR increase (mL/min) = Post-donation mGFR - (mGFR pre-donation / 2)

The renal vascular resistance (RVR) is calculated as described previously(7, 14):
RVR (in dynes*second*centimeter^{-5})= Mean Arterial Pressure / RBF
Where RBF is the Renal Blood flow, calculated as:
ERPF / (1 – hematocrit)

Statistical analysis

Data are reported as mean (standard deviation) for normally distributed variables and median [interquartile range] for skewed data. Binary variables are shown as "number (%)". GFR data are reported as absolute values (mL/min) and normalized for body surface area (BSA; mL/min/1.73m^2). We used linear regression analysis to investigate the association between pre-donation RFR_{dopa} with post-donation compensatory GFR increase and with pre- and post-donation GFR. We also investigated the association between pre-donation RFR_{dopa} and GFR change (defined as: post-donation mGFR / pre-donation mGFR *100%). We adjusted for age and sex as potential confounders. Statistical analyses were performed using SPSS version 22 for Windows (IBM, Armonk, NY), R version 3.0.1, and Graphpad Prism 6 for Windows (Graphpad, San Diego, CA). P-values of <0.05 were considered statistically significant.

Results

Pre-and post-donation characteristics

We included 937 living kidney donors who were 52±11 years old at donor screening, 484 (52%) were female. Before donation, mean GFR was 114±22 mL/min, which increased to 124±24 mL/min after stimulation with dopamine, resulting in a pre-donation Renal Functional Reserve (RFR_{dopa}) of 9±10 mL/min. Three months after donation mean single-kidney GFR was 72±15, rising to 75±15 mL/min after dopamine, resulting in a post-donation RFR_{dopa} of 3±6 mL/min. The compensatory GFR increase after donation (expressed increase of GFR above 50% of pre-donation GFR) was 15±9 mL/min. In 20 donors (3%) albuminuria was present prior to donation with a median pre-donation albumin excretion of 46 [37;78] mg/24h (23 [19;39] per kidney). Post-donation albuminuria at 3 months after donation (34 donors, 6%) was 44 [38;76] mg/24h. Other pre- and post-donation characteristics are shown in Table 1. Pre-donation RFR_{dopa} was associated with the compensatory GFR increase early after donation, independent of possible confounders (st. β 0.18, P<0.001; Figure 1). Other independent determinants of the compensatory GFR increase were age (st. β -0.32, P<0.001) and BSA (st. β 0.14, P=0.002), whereas the pre-donation GFR was negatively associated with the compensatory GFR increase (st. β -0.13, P=0.003). In a multivariable analysis BSA was a better predictor of the compensatory GFR increase than BMI.

Table 1. Characteristics of the living kidney donors

Variable	Number	Pre-donation	Post-donation	*P-value*
Age (years)	937	52 ± 11	53 ± 11	*<0.001*
Female sex, n (%)	937	484 (52)	484 (52)	*N/A*
Systolic blood pressure (mmHg)	927	127 ± 13	124 ± 13	*<0.001*
Diastolic blood pressure (mmHg)	927	76 ± 9	76 ± 9	*0.73*
Use of antihypertensives, n (%)	893	135 (15%)	144 (16%)	*q*
- ACE inhibitors	892	51 (6%)	49 (6%)	*0.75*
- ARBs	893	29 (3%)	28 (6%)	*1.00*
- Thiazides	893	43 (5%)	48 (5%)	*0.13*
- Beta blockers	893	50 (6%)	59 (7%)	*0.01*
- Calcium antagonists	893	27 (3%)	30 (3%)	*0.51*
Height (meters)	937	175 ± 9	175 ± 9	*<0.001*
Weight (kilogram)	906	80 ± 14	8 ± 13	*<0.001*
Body mass index (kg/m^2)	906	26 ± 4	26 ± 3	*<0.001*
GFR (mL/min)	937	114 ± 22	72 ± 15	*<0.001*
GFR/$_{BSA}$ (mL/min/1.73m^2)	904	101 ± 16	64 ± 11	*<0.001*
GFR per kidney† (mL/min)	937	57 ± 11	72 ± 15	*<0.001*
GFR after dopamine (mL/min)	903	124 ± 24	75 ± 15	*<0.001*
GFR after dopamine per kidney† (mL/min)	903	62 ± 12	75 ± 15	*<0.001*
RFR$_{dopa}$ (mL/min)	903	9 ± 10	3 ± 6	*<0.001*
RFR$_{dopa}$ (%)	903	8 ± 9	4 ± 8	*<0.001*
RFR$_{dopa}$ per kidney† (mL/min)	903	5 ± 5	3 ± 6	*<0.001*
RFR$_{dopa}$ per kidney (%)	903	4 ± 4	4 ± 8	*0.22*
Compensatory GFR increase (mL/min)	937	N/A	15 ±9	*N/A*
Compensatory GFR increase (%)	937	N/A	27 ±16	*N/A*
ERPF (mL/min)	931	378 ± 90	256 ± 61	*<0.001*
ERPF/$_{BSA}$ (mL/min/1.73m^2)	903	335 ± 72	226 ± 46	*<0.001*
ERPF after dopamine (mL/min)	902	450 ± 121	291 ± 73	*<0.001*
Filtration fraction (proportion)	931	0.31 ± 0.05	0.29 ± 0.04	*<0.001*
Proteinuria (>300 mg/24h), n (%)	711	28 (4%)	27 (4%)	*1.00*
Albuminuria (>30 mg/24h), n (%)	604	20 (3%)	34 (6%)	*0.04*

N, Number; ACE inhibitors, Angiotensin-Converting Enzyme inhibitor; ARBs, Angiotensin Receptor Blockers; BSA, Body Surface Area; mGFR, measured Glomerular Filtration Rate; RFR$_{dopa}$, Renal Functional Reserve by dopamine; ERPF, Effective Renal Plasma Flow

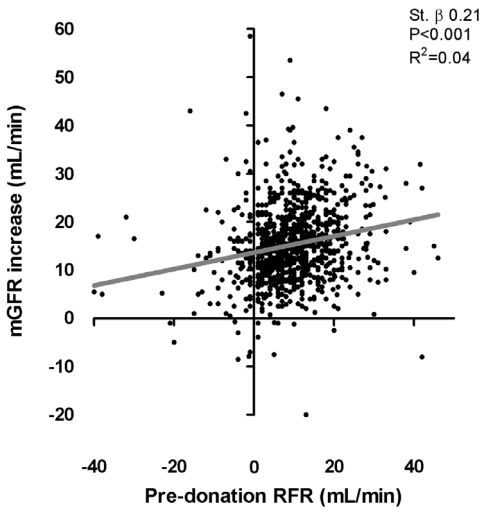

Figure 1. Association between pre-donation RFR and short-term GFR increase
The pre-donation RFR_{dopa} is associated with the compensatory GFR increase shortly after donation (st. β 0.21, P<0.001), defined as the GFR increase relative to 50% of its pre-donation value. This indicates that donors with a higher pre-donation RFR_{dopa} have a higher compensatory GFR increase early after donation. The regression line is calculated using ordinary least squares regression.

Pre-donation RFR_{dopa}, Renal Hemodynamics and Renal Vascular Resistance

In response to dopamine, most donors had an increase of effective renal plasma flow (change $ERPF_{dopa}$, 72±52 mL/min (P<0.001), a decrease in renal vascular resistance (RVR) and filtration fraction (change $FF_{dopa,}$ -3±2%). One hundred and six donors (11%) had a negative RFR_{dopa}, (ie a decrease in GFR during dopamine). In these donors the decrease in FF was significantly larger than in donors with a positive RFR_{dopa} (-4±3% versus -2±2%, P<0.001). Mean renal vascular resistance (RVR) was 11889±3039 dynes*sec*cm^{-5} in all donors and decreased to 10132±2842 dynes*sec*cm^{-5} after dopamine. In donors with a negative RFR_{dopa}, the decrease in RVR was significantly less than in donors with a positive RFR_{dopa} (-659±1282 versus -1910±1023 dynes*sec*cm^{-5}, P<0.001).

Pre-donation RFR_{dopa} and GFR 3 months post-donation

The pre-donation RFR_{dopa} was not associated with pre-donation GFR (st. β -0.009, P=0.77) in the 937 living kidney donors (Figure 2A) and was even negatively associated after adjustment for age and sex (st. β -0.06, P=0.04). However, there was a significant positive association between the pre-donation RFR_{dopa} and the change of GFR after nephrectomy (from pre-donation to 3 months post-donation; st. β 0.15, P<0.001; Figure 2B). This association remained significant after adjustment for age, sex, body surface area, 24 hour

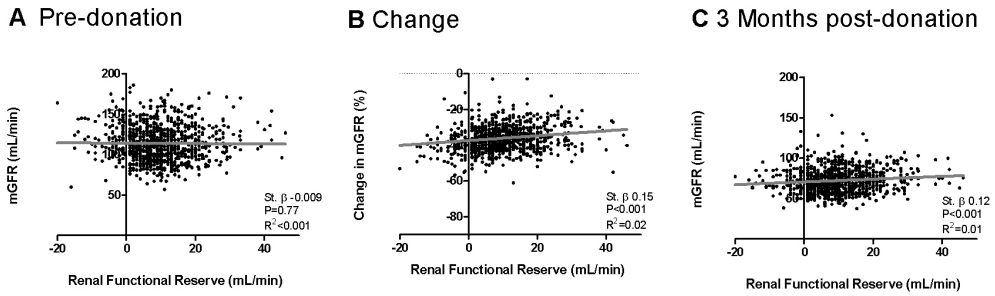

Figure 2: Association between pre-donation RFR and GFR three months post-donation
The pre-donation RFR_{dopa} was not associated with pre-donation GFR (st. β -0.009, P=0.77)**(A)**. It was associated with the change in mGFR after donation (st. β 0.15, P<0.001) **(B)** as well as with the absolute GFR at three months post-donation (st. β 0.12, P<0.001)**(C)**. The regression lines are calculated using ordinary least squares regression.

sodium excretion, blood pressure, use of antihypertensive medication, albuminuria and GFR (final model; st. β 0.18, P<0.001, R^2 0.60). Consequently, the pre-donation RFR_{dopa} was associated with the GFR at 3 months post-donation (st. β 0.12, P<0.001; Figure 2C), which remained significant after adjustment for potential confounders (st. β. 0.15, P<0.001). When the RFR_{dopa} was expressed as percentage of the pre-donation GFR the association lost statistical significance (st. β -0.02, P=0.47).

Pre-donation RFR_{dopa} and GFR 5 years post-donation

In 383 donors with a follow-up of ≥5 years (median 5.1 [5.0-5.4] years), pre-donation GFR was 116±22 mL/min and RFR_{dopa} was 10±11 mL/min. At 5 years post-donation the GFR in these donors was 78±16 mL/min. Other characteristics of this group are shown in Table 2. There was an association between the pre-donation RFR_{dopa} and GFR change from pre-donation to 5 years post-donation (st. β 0.14, P=0.008). This association, however, was lost after adjustment for age, sex, body surface area, 24 hour sodium excretion, blood pressure, use of antihypertensive medication, albuminuria and GFR (final model; st. β 0.04, P=0.45, R^2 0.45). We found no association between the RFR_{dopa} and change in mGFR between 3 months to 5 years post-donation (st. β -0.09, P=0.09), while age was a predictor of this change (st. β -0.19, P<0.001). We also found no association between pre-donation RFR_{dopa} and GFR at ≥5 years post-donation (st. β 0.05, P=0.35). The change in pre-donation FF in response to dopamine was not associated with GFR at ≥5 years post-donation (st. β -0.06, P=0.29), but the change in RVR in response to dopamine was associated with GFR at ≥5 years post-donation (st. β 0.34, P<0.001). However, this association was lost after adjustment for pre-donation GFR (st. β 0.04, P=0.26).

Table 2. Characteristics of donors with long-term follow-up

Variable	Number	Pre-donation	Long-term	*P-value*
Follow-up after donation	383	0	5.1 [5.0-5.4]	
Age (years)	383	50 ± 10	57 ± 10	*<0.001*
Sex, n (%) female	383	210 (55%)	210 (55%)	*N/A*
Systolic blood pressure (mmHg)	376	127 ± 14	127 ± 14	*0.65*
Diastolic blood pressure (mmHg)	376	76 ± 9	76 ± 9	*0.28*
Use of antihypertensives, n (%)	317	53 (17%)	97 (31%)	*<0.001*
ACE inhibitors	317	32 (10%)	34 (11%)	*0.85*
ARBs	317	9 (3%)	36 (11%)	*<0.001*
Thiazides	317	15 (5%)	26 (8%)	*0.04*
Beta blockers	317	23 (7%)	39 (12%)	*0.004*
Calcium antagonists	317	7 (2%)	16 (5%)	*0.02*
Height (meters)	383	174 ± 9	173 ± 9	*<0.001*
Weight (kilogram)	381	80 ± 14	82 ± 15	*<0.001*
Body mass index (kg/m^2)	381	26 ± 4	27 ± 4	*<0.001*
GFR (mL/min)	383	116 ± 22	78 ± 16	*<0.001*
GFR/$_{BSA}$ (mL/min/1.73m^2)	381	104 ± 16	69 ± 12	*<0.001*
GFR per kidney† (mL/min)	383	58 ± 11	78 ± 16	*<0.001*
GFR after dopamine (mL/min)	383	126 ± 25	N/A	*N/A*
GFR after dopamine per kidney† (mL/min)	383	63 ± 12	N/A	*N/A*
RFR$_{dopa}$ (mL/min)	383	10 ± 11	N/A	*N/A*
RFR$_{dopa}$ (%)	383	9 ± 9	N/A	*N/A*
RFR$_{dopa}$ per kidney† (mL/min)	383	5 ± 5	N/A	*N/A*
RFR$_{dopa}$ per kidney (%)	383	5 ± 5	N/A	*N/A*
ERPF (mL/min)	381	407 ± 93	263 ± 58	*<0.001*
ERPF/$_{BSA}$ (mL/min/1.73m^2)	379	362 ± 76	232 ± 46	*<0.001*
ERPF after dopamine (mL/min)	381	496 ± 124	N/A	*N/A*
Filtration fraction (proportion)	381	0.29 ± 0.05	0.30 ± 0.03	*<0.001*
Proteinuria (>300 mg/24h) n (%)	266	12 (5%)	7 (3%)	*0.36*
Albuminuria (>30 mg/24h) n (%)	76	2 (3%)	7 (9%)	*0.13*

ACE inhibitors, Angiotensin-Converting Enzyme inhibitor; ARBs, Angiotensin Receptor Blockers; BSA, Body Surface Area; mGFR, measured Glomerular Filtration Rate; RFR$_{dopa}$, Renal Functional Reserve by dopamine; ERPF, Effective Renal Plasma Flow

Discussion

In this study we show that pre-donation dopamine-recruited Renal Functional Reserve (RFR$_{dopa}$) is associated with the compensatory GFR increase 3 months after donation and with GFR at 3 months post-donation, but not with GFR at 5 years post-donation. These results indicate that, while the RFR$_{dopa}$ is a predictor of the short-term hemodynamic changes

after living kidney donation, it has no value as a predictor of long-term renal function in living kidney donors. Therefore, measurement of RFR_{dopa} is not a useful screening tool for living kidney donors.

Upon kidney donation, living donors lose approximately 50% of their nephron mass and hence renal function, but almost directly increase their GFR up to 60-75% of their pre-donation value by using their renal functional reserve (4). In the 5 to 15 years thereafter, the GFR continues to rise slowly, followed by a normal age-related decline afterwards (12, 13). The RFR_{dopa} was thought to predict the ability of the kidney to increase its GFR as a compensatory response to nephrectomy (22, 24). In line with this assumption we show that the RFR_{dopa} is associated with the compensatory GFR increase after donation and with short-term GFR, and thereby is a predictor of the early hemodynamic changes after living kidney donation. This matches the mechanism of action of the dopamine response, as dopamine induces renal vasodilatation and hence a GFR increase(8, 23). Interestingly, some donors had a negative RFR_{dopa}, meaning a decrease in GFR after dopamine. We show that this was due to a relatively large decrease in Filtration Fraction (FF) and a relatively small decrease in Renal Vascular Resistance (RVR) in response to dopamine compared to donors with a positive RFR_{dopa}. We are well aware that clearance measurements only allow indirect inferences on the responses of the renal microvasculature, but this response pattern could suggest that a decrease in GFR during dopamine is due to a predominantly efferent vasodilator response, with a blunted afferent vasodilation(8, 23). The decrease in RVR was associated with GFR after donation in univariable analysis, but this association was lost after adjustment for pre-donation GFR. Further studies are needed to study changes in RVR after living kidney donation.

While predictive of the hemodynamic response early after kidney donation, the response to dopamine was neither a predictor of the increase in GFR long-term post-donation nor of the absolute GFR at 5 years post-donation. This supports the assumption that the gradual GFR increase in most donors in the 5-15 year period after donation is mechanistically different from the short-term hemodynamic response(4, 18). We hypothesize that the long-term GFR increase reflects more structural changes in single remaining kidney, which may include benign increase of glomerular size(6), tubulo-interstitial hypertrophy(26) and changes in recruitment of renal arteries(9). As reported before, we found that this gradual GFR increase is dependent on donor age(11). Since the RFR_{dopa} was unable to predict these changes, it is not a suitable screening tool for living donors to predict long-term outcomes. Studies of other possible predictors of long-term renal changes are warranted, since the long-term changes in renal function may be a main driver of the increased risk of renal failure in living kidney donors(1, 10, 11, 13).

Limitations of our study are the single-center nature and that the majority of donors were Caucasian, making conclusions about the RFR_{dopa} not generalizable to other ethnicities. Furthermore, our results reflect renal hemodynamics in accepted donors and we have no data on the long-term GFR in rejected donor candidates. We also were unable to study the relation of RFR_{dopa} with GFR beyond five years post-donation. Strengths of our study include the extensive renal hemodynamic measurements using continuous ^{125}-iothalamate and ^{131}-Hippuran infusions pre- and post-donation(2).

In conclusion, pre-donation RFR_{dopa} is a predictor of the compensatory GFR increase after donation and of short-term renal adaptation after living kidney donation, but not of long-term renal adaptation. Therefore, measurement of the RFR_{dopa} is not a valid tool for living donor screening. Studies investigating long-term renal adaptation are warranted to study the effects of living kidney donation and to improve donor screening.

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Disclosures

The authors have no relevant conflicts of interest to declare.

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PART TWO

Living Donation Beyond the GFR